Fatal Aplastic Anemia Following Chloramphenicol (Chloromycetin) Therapy

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CHLORAMPHENICOL (Chloromycetin®) was first produced in 1947 from the soil actinomycete[5] and has been shown to be effective clinically against many organisms pathogenic in humans. Ease of administration, availability, moderate cost and the low incidence of gastrointestinal irritation associated with it have contributed to widespread use of the drug. These would be favorable attributes of any therapeutic agent, yet they could be nullified to a great extent if the agent in question had a considerable degree of toxicity, even though injury from it occurred infrequently.

Following is a report of a case of fatal aplastic anemia that developed after six weeks of therapy with chloramphenicol.

CASE REPORT

A 35-year-old white married woman was admitted to the French Hospital on March 7, 1952, because of generalized icterus, anorexia and lassitude. The illness had begun Jan. 10, 1952, with fever, chills and symptoms of irritation of the bladder. These symptoms were intermittent for the next ten days, and the patient was examined in the urological department of the hospital on January 23. A specimen of urine obtained by catheter had specific gravity of 1.005 and contained a trace of albumin. There were 5 erythrocytes per high power field, occasional leukocytes and epithelial cells. A culture was negative for acid-fast bacilli, but on it grew organisms morphologically and biochemically resembling Pseudomonas aeruginosa.

The patient received one injection of 400,000 units of procaine penicillin on January 23 and chloramphenicol, 250 mg. thrice daily, was prescribed. An intravenous urogram and x-ray of the chest on Jan. 24 were reported as within normal limits. When observed Jan. 30 and Feb. 6 the patient said she felt a great deal better. A nine-hour sample of urine was examined by Addis' method on Feb. 1, 1952. The following was reported: Total quantity 850 cc., specific gravity 1.005, acid reaction, albumin quantitative 1.7 gm., erythrocytes 136,666, casts 700, and leukocytes 666.

On Feb. 22 chills, fever and sweating developed, lasted one day, and were followed by malaise, anorexia, nausea and weakness. Jaundice was first noted by the patient on March 1. It increased gradually until admittance to hospital on March 7.

In the six weeks preceding admittance to the hospital the patient had taken a total of approximately 30 gm. of chloramphenicol and no other medication.

Past History. Chronic glomerular nephritis had existed since 1947, apparently a result of streptococcal infection of the throat in 1946. The patient had been rather closely observed in the interim, during which she carried out the duties of a housewife and mother in a normal manner, and objective studies from time to time indicated very little progression of renal disease. Specimens of urine were constantly of low specific gravity. Mild proteinuria was present, and occasionally hematuria was noted microscopically. Intravenous urograms were normal except for somewhat faint concentration of dye. Hemograms were within normal limits. The blood pressure varied from 130 mm. of mercury systolic and 96 mm. diastolic to 150 mm. and 104 mm. respectively. In December 1950 the urea nitrogen content of the blood was 15 mg. per 100 cc. In December 1950 abortion was done as a precautionary measure in view of the renal disease.

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Upon physical examination March 7, 1952, the patient was observed to be well developed and well nourished. She was not in acute distress, but pronounced jaundice was present. The edge of the liver was palpable two fingers' breadth below the right costal margin and it was slightly tender on percussion and deep palpation. Temperature, pulse and respirations were normal. The blood pressure was 140 mm. of mercury systolic and 90 mm. diastolic. Erythrocytes numbered 4,070,000 per cu. mm. and the hemoglobin content was 12.4 gm. per 100 cc. Leukocytes numbered 6,100—68 per cent neutrophils and 32 per cent lymphocytes. Platelets were reported as normal. Urinalysis showed specific gravity of 1.003, a trace of albumin, no sugar, one plus bile, two to four leukocytes per high dry field, and many epithelial cells.

Prothrombin time was 82 per cent of normal. The icteric index was 115 units, thymol turbidity 28 units, urinary urobilinogen 1.26 Ehrlich units, serum cholesterol content 210 mg. per 100 cc., total protein content in the serum 8.6 gm. per 100 cc. (albumin 3.3 gm. and globulin 5.3 gm.), serum bilirubin content 14.3 mg. per 100 cc. (direct reaction 2.3 mg. per 100 cc.) Cephalin flocculation was two plus.

A diagnosis of viral hepatitis was made. The patient was kept in bed and a diet high in protein, carbohydrate and vitamins was prescribed. Thiamine chloride, 10 mg. daily, was given and there was no other medication. The patient made excellent progress and on March 21 the icteric index was 22 units, thymol turbidity 9.5 units, and the urine negative for bile.

On the same day, the patient noted a few petechiae on her arms and attributed them to scratching. Next day the number of petechiae had increased, but the patient said she felt well. On this day bleeding time was 1½ minutes and clotting time 7 minutes. The following evening, March 23, catamenia began and became profuse. A persistent cough productive of a bloody sputum developed and there were increasing numbers of petechiae and areas of ecchymosis over the entire body. Erythrocytes numbered 1,450,000 and the hemoglobin content was 4.6 gm. per 100 cc. of blood. The cell volume was 14 per cent of the whole blood. Leukocytes numbered 3,200—51 per cent neutrophils and 48 per cent lymphocytes. No platelets were observed in the blood. Bleeding time was 5 minutes, clotting time 12 minutes, and there was no clot retraction in 8 hours. Urinalysis showed three plus albumin, no sugar, 40 to 50 erythrocytes per high dry field and specific gravity of 1.010. Erythrocyte fragility was normal and the result of Coombs' test was negative. The sternal marrow was hypoplastic and no megakaryocytes were noted in it. No marrow substance could be aspirated from the spinous process in two attempts.

Following are data on results of examination of the blood at various times during the last period of hospitalization:

Date 1952	Hemoglobin gm. per 100 cc.	Erythrocytes (Per cubic millimeter)	Leukocytes (Per cubic millimeter)	Platelets (Per cubic millimeter)	Leukocyte differential (per cent) Neutrophils	Lymphocytes	Eosinophils
Mar. 7	12.4	4,070,000	6,100	Normal	68	32	
Mar. 24	4.6	1,450,000	3,200	None seen	51	48	1
Mar. 25	9.2	3,160,000	2,200	None seen	43	53	4
Mar. 26	12.	3,960,000	1,100	11,000	41	59	
Mar. 28	11.	3,640,000	1,200	Too few for accurate count	28	71	1

Six 500 cc. transfusions of whole blood, including 1,500 cc. of fresh whole blood, were given between March 24 and March 26, but the condition of the patient deteriorated rapidly. The pulse rate rose to 120 per minute. Respirations were shallow and labored and the rate 40 per minute. The rectal temperature reached 103° F. New showers of petechiae appeared daily, and gross melena, epistaxis, gingival bleeding, hemoptysis and vaginal bleeding continued. The patient became progressively weaker and died March 29.

In addition to blood transfusions and general supportive measures, the patient was given penicillin, 600,000 units daily, corticotropin (ACTH), caffeine sodium benzoate, and oxygen both by mask and positive pressure.

NECROPSY

The skin of the entire body was faintly icteric, and over the skin of the trunk, the extremities and the abdomen were multiple purpuric areas 3 mm. to 10 mm. in diameter. Multiple purpuric areas were present over the surface of the diaphragm, along the wall of the stomach and on the mucosal and serosal surfaces of the small bowel. Semi-liquid, black tarry fecal matter was present in moderate amount in the terminal ileum and in progressively greater quantity distally to the colon. No evidence of ulcer or neoplasm was noted in the gastrointestinal tract, which was patent throughout.

Sections of bone marrow from the sternum and vertebrae were essentially similar histologically. Fat cells were predominant with sparsely scattered clusters of myeloid elements lying between. The distribution was not uniform, some areas approaching a normal degree of cellularity and other areas being entirely adipose. In most regions there were at least a few marrow elements between the fat cells. There were representatives of all constituents present, but the lymphocytic series was more prominent. Megakaryocytes were rare.

The heart weighed 275 gm. The external surface of the pericardium was smooth and the pericardial cavity contained a small amount of straw-colored fluid. The cardiac chambers, endocardial surface, valve leaflets and coronary vessels showed no abnormalities. Microscopically the cardiac muscle fibers appeared of normal size and shape with no evidence of infiltration or scarring of the myocardial tissue.

The left lung weighed 575 gm., the right 975 gm. Both pleural cavities contained minimal amounts of straw-colored fluid. The mucosa of the bronchi was deep pink and copious amounts of fluent blood were present in the lumen. The parenchyma of the lungs was deeply mottled, with a deep, shiny, blackish purple the predominant color. Only near the apices were there small areas resembling normal lung tissue. Both lungs were hypocrepitant and had a solid hepatic feeling on palpation. Cut sections revealed approximately 80 per cent of the lung mass to have a deep purple, solid appearance, with small purple, jelly-like clots emerging from the surface. On microscopic examination the normal architecture of the pulmonary tissue was almost entirely obscured. In some areas massive amounts of red cells and a pink-staining, homogenous material filled the alveoli and some segments appeared entirely airless. No evidence of tumor was noted.

The spleen weighed 125 gm. The capsule was smooth and of uniform slate-gray color. On section the surface appeared uniformly firm, and malpighian corpuscles were evenly distributed throughout the parenchyma. Microscopically the architecture of the spleen appeared to be within normal limits.

The liver weighed 1,500 gm. The external surface was smooth and glistening. The margins were sharp and well defined. Sections were a normal reddish-brown, and lobular markings were clearly visible. A normal lobular pattern was present, with slight thickening of the portal triads, but no extension of these structures. The thickening was due chiefly to lymphocytic infiltration involving about one-half of the triads. Slight fibroblastic proliferation was noted. The most striking feature was disarray of lobules in many areas. The liver cords, particularly at the lobular centers, were obscured and the liver cells haphazard in disposition. They were variable in size and shape with occasional multinuclear forms. Also noted at the lobular centers, quite commonly, were dilated canaliculae containing bile thrombi. These were seen in every second or third lobule. The sinusoids were not distended. The Kupffer cells were enlarged, and many contained brown granular pigment, apparently hemosiderin.

The gallbladder was a turgid, deeply mottled, dark purple sac. It contained a quantity of purplish, jelly-like clots and

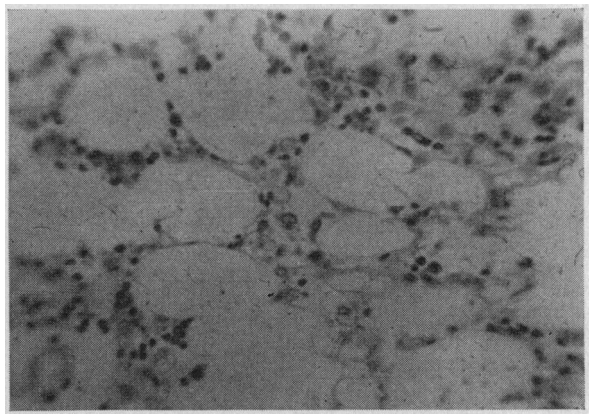

Figure 1.—Bone marrow (high power) showing acellularity.

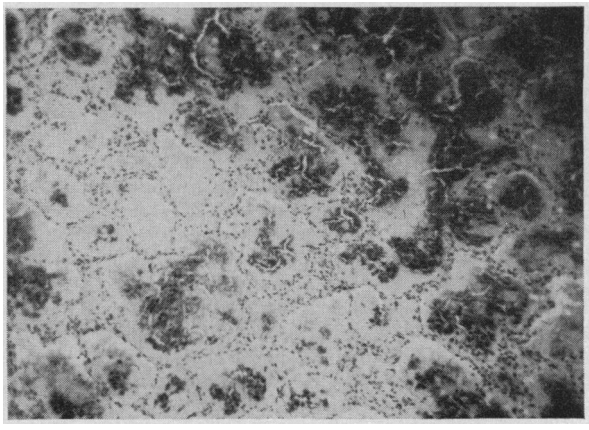

Figure 2.—Lung (low power). Note hemorrhage into alveoli.

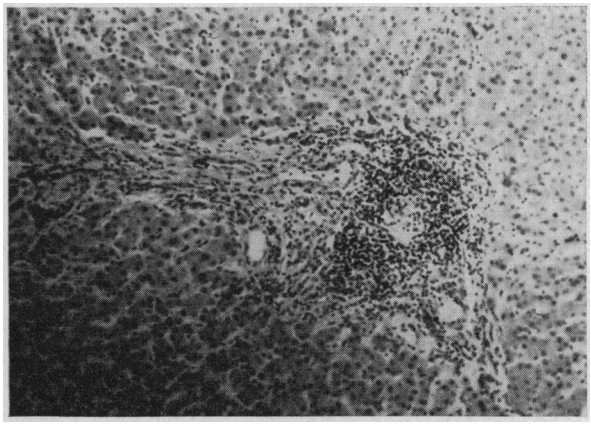

Figure 3.—Liver (high power). Note periportal round cell infiltration.

viscid purplish-black mixture of blood and bile. There were large amounts of blood within the fibers of the muscular coat and infiltrating into the mucosal layer. No stones or tumors were present in the gallbladder or common duct.

The adrenal glands were grossly normal. Microscopically the usual pattern of the glands did not appear to be disturbed.

Each kidney weighed 118 gm. The capsules were stripped with ease, revealing finely pebbled or granular surfaces, which were diffusely covered with small dark purpuric nodules approximately 1 mm. or less in diameter. Many of the glomeruli had undergone partial or complete hyalinization. Those which were not involved were enlarged and excessively cellular. Occasional remnants of crescents were noted and there was capsular adhesion at many points. The convoluted tubules were disposed in clusters of dilated elements separated by areas of lymphocytic infiltration and fibrosis in which the tubules were greatly diminished. The dilated lumina contained hyalin and acidophilic casts. The glomerular capillaries were narrowed where hyalinization had not supervened. Symmetrical thickening of the walls of the smaller divisions of the arterial tree was noted, whereas the larger divisions were relatively free of sclerotic change. There was little inflammatory infiltration in the medulla and the pelvic membranes were uninvolved.

The final diagnosis was: 1. Marked hypoplasia of the bone marrow; 2. Chronic glomerulonephritis; 3. Subacute hepatitis; 4. Massive tissue hemorrhage into lung parenchyma, bilateral.

DISCUSSION

It seems clearly established that aplastic anemia with the typical clinical manifestations and changes in the bone marrow and peripheral blood may be produced by a variety of toxic substances.[19] This so-called secondary aplastic anemia differs in no way clinically or histologically from the idiopathic form, which by many observers is regarded as also caused by irreversible chemical injury from an unrecognized source[21] or possibly actually representing the marrow of aleukemic leukemia. It is sometimes difficult to prove conclusively that an etiological relationship exists between the disease state and the potentially toxic substance to which the person is exposed.

In some instances, as is the case in the etiological relationship of benzol and its derivatives, arsphenamine, irradiation, trinitrotoluene, and a few others, the evidence is so overwhelming as to be conclusive.[19] There are varying degrees of susceptibility. Some persons react violently, others slightly or not at all. A native idiosyncrasy to a drug may exist or sensitization may develop after long exposure or repeated short exposures. The concentration or the total amount of the suspected agent may be an important factor in the development of the adverse reaction.

Any substance which contains the nitrobenzene radical should be regarded with suspicion;[3] and Smadel[16] pointed out the presence of this radical in the structure of chloramphenicol and warned of its possible toxic effect on the hematopoietic system.

In attempting to evaluate the role played by any suspected therapeutic agent in the production of toxic effects, it is necessary to consider the possible etiological relationship of the disease state being treated as well as the effects of other drugs being administered. The patient here reported upon was known to have had chronic glomerular nephritis for the preceding five years, but there was very little evidence clinically of progression of the renal disease. It is well known that anemia is a fairly common complication late in nephritis, more commonly with the advent of uremia. The exact mechanism is not clear, but a depressant effect on the hematopoietic system by retained toxic metabolites is considered most likely.[1] However, the development of an acute fulminating episode on the basis of preexisting renal impairment of the degree described would indeed be exceedingly unusual.

Another factor which must be evaluated in the present case is the hepatitis which developed approximately four weeks after treatment with chloramphenicol was begun. The list of chemical substances capable of causing liver damage is quite extensive, and among the aromatic compounds, nitrobenzene has been shown to possess this property. Clinically, the manifestations of hepatitis are the same whether the etiological factor be toxic or viral. Differentiation depends on the history and histological studies. Lichtman[10] stated that in non-fatal viral hepatitis the lesions are generally zonal in distribution and cell necrosis extremely rapid. Cellular reaction is non-leukocytic and periportal cellular infiltrates consist primarily of round cells and eosinophils. In toxic hepatitis, cellular necrosis is gradual; that is, more coagulative. The usual pattern of destruction is not zonal, because the poisonous agent attacks the entire lobule with equal severity, producing all stages of cellular disintegration. In regions which remain intact, the inflammatory reaction consists largely of neutrophils. Lepper and co-workers[9] produced histologic changes in the livers of mice and dogs by administering large doses of aureomycin, of terramycin and of chloramphenicol. Rich and co-workers,[14] in a report of a fatal case of aplastic anemia following chloramphenicol therapy, described scattered foci of liver necrosis noted at necropsy. As jaundice had not developed, they regarded the necrosis as a late event and they stated that foci of hepatic necrosis develop in some cases of marrow aplasia regardless of cause.

In a search of the recent literature no report of an instance of toxic hepatitis resulting from the therapeutic administration of chloramphenicol was found, and it seems quite likely that the patient in the present case had infectious hepatitis; both the clinical course and the histologic changes in the liver were entirely consistent with that condition—in fact were more suggestive of it than of primary toxic disease.

The possibility that hepatitis induced the bone marrow aplasia seems exceedingly remote, especially in view of the clinical course and histological observations. Post, Gellis and Lindenauer[13] in studies of the sequelae of acute infectious hepatitis in 114 patients made no mention of aplastic anemia.

In reviewing factors that might have caused the changes in the bone marrow, then, consideration must be given to chloramphenicol. It has been shown by repeated animal experiments that the subcutaneous injection of benzene will produce a depression of the bone marrow and concomitant reduction of the leukocytes in the blood to 200 or 300 per cu. mm., with complete absence of granulocytes.[8] Dietz and Steinberg[4] in a report on a study of the chemical composition of rabbit bone marrow in benzene poisoning stated the action of benzene on the marrow was to increase its water content and to decrease the amount of lipid, total and non-protein nitrogen and non-protein sulfur fraction.

In the past two years there have not been a great many reported instances of bone marrow depression following the use of chloramphenicol, but they seem to be on the increase. Volini and co-workers[20] reported the development of bone marrow hypoplasia in three patients treated with chloramphenicol for periods of nine to nineteen days during which the total amounts given were 26 to 53 grams. Granulocytopenia developed in all, with involvement of the erythrocyte element in one. All responded favorably when use of the drug was discontinued. Gill[6] reported the development

of granulocytopenia in two infants treated with the drug. One of them received approximately 6 grams in 12 days and the other 2 grams in 2 days. Both recovered when use of the drug was stopped. Rich and co-workers[14] reported a case in which fatal aplastic anemia developed in a 63-year-old male who received 57 grams of chloramphenicol over a period of three months for a chronic urinary tract infection. Loyd[11] reported a case of fatal aplastic anemia following treatment with chloramphenicol intermittently over a period of one and one-half years for a urological disorder. The amount of the drug given was not stated. Two cases of aplastic anemia (one resulting in death) following prolonged use of chloramphenicol were reported by Wilson and co-workers.[22] Both patients received 2 grams weekly (one for 28 weeks and the other for 26 weeks) in treatment for chronic bronchopulmonary suppuration. Patterson[12] reported a case in which severe anaphylactic shock, which required heroic measures to overcome, developed a half hour after 500 mg. of chloramphenicol was administered.

In light of the clinical events, hematopoietic changes and necropsy findings in the present case and in the reports of other observers, the preponderance of evidence appears to incriminate chloramphenicol as a potentially noxious agent capable of inducing severe myeloid depression. In considering associated factors influencing the development of hematologic changes by this agent, length of administration and total dosage must be evaluated.

In the present case the patient received approximately 30 grams over a six-week period—less of the drug and in a shorter period than in any of the other three reported fatal cases. Certainly, thousands of patients have received larger amounts and for greater lengths of time without toxic effect. Gray[7] estimated the incidence of blood dyscrasia concomitant with chloramphenicol therapy at 1 in 400,000. It is worthy of note that in three of the four fatal cases the patients were taking chloramphenicol for a urological disorder. Does impaired renal function play a role in the production of toxic effects by the drug? One must consider the possibility that associated pathologic conditions complicate the disease for which chloramphenicol therapy is given. Possibly patients with impaired renal or hepatic function should not take the drug unless the hematologic effect can be very closely observed. Length of administration may be an important factor, but it would seem from the evidence in the present case that individual idiosyncrasy, or at least hypersensitivity, plays a more vital role.

Other observers[14, 20, 11, 22] have suggested frequent examinations of the blood during therapy with chloramphenicol and discontinuance of the drug at the first sign of depression in granulocytes, erythrocytes or thrombocytes.

In the case here reported the hemogram was normal when the patient entered the hospital and no chloramphenicol was given from that time on. At least in this instance frequent examination of the blood during therapy with the drug would seemingly have furnished little or no warning of impending events. It is regrettable that there was no examination of the blood between the time of admittance and the appearance of purpuric manifestations, two weeks after cessation of therapy with chloramphenicol. However, at that time the patient seemed to be making uneventful recovery from hepatitis and there was no suspicion of toxic effects from previous therapy.

From the standpoint of preventing or modifying the toxicity of benzene and nitrobenzene compounds, Shils and Goldwater[15] conducted some interesting animal experiments. They conclude that, from a practical nutritional point of view, special emphasis should be placed on eating well-balanced meals containing a good proportion of high quality protein and they expressed belief it is probably wise to keep the fat intake at moderately low levels.

It would certainly seem unwise to condemn a drug which has proven its effectiveness against a large group of infections, some of which entail a high degree of morbidity and mortality, merely because of the occasional occurrence of untoward effects. Many lives have been saved and much suffering and loss of time have been eliminated by the judicious use of some of the newer drugs in treating disease states, for which there had been previously no specific or effective therapy. If occasionally in such an instance, despite the observance of all known precautions, an untoward effect results from the therapy, it is regrettable but excusable.

ADDENDUM

Since this report was prepared there have appeared in the literature three papers with the accounts of eight additional deaths from aplastic anemia following therapy with chloramphenicol.[2, 17, 18] From the increasing number of reports of bone marrow depression associated with the use of this product, it seems mandatory that a definite stand be taken with regard to its employment in the future.

In the author's opinion, it should be prescribed only in those situations where the life of the patient is threatened and where no other type of therapy, with a less toxic potential, has proven to be effective. If all physicians using it are aware of its possible deleterious action, if self-medication by patients is prohibited, and if the blood is continuously scrutinized during use of the drug and for several weeks after it is discontinued, many of the dire results might be avoided.

SUMMARY

A fatal case of aplastic anemia following chloramphenicol therapy is reported, together with necropsy findings. The possible etiologic relationship of a preexisting chronic glomerular nephritis and coexistent hepatitis is discussed. Closer observation of the hematopoietic system during use of the drug is suggested.

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Acute Exfoliative Dermatitis Due to Dormison®

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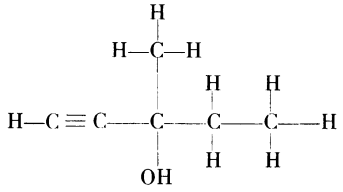
ALTHOUGH even good drugs have dangers and limitations, especially hypnotics which are in great popular demand, considerably more was written about Dormison® in the lay press for the general public than was available to physicians in medical literature when the drug was introduced for sale. In an exhaustive search of recent medical literature only two articles specifically relating to this drug were found, while between October and Christmas 1951, a rash of popular articles appeared in such magazines as the *Woman's Home Companion, Cosmopolitan, Collier's* and *Reader's Digest.*

Tertiary carbinols have long been known to produce central nervous system depression.[1] Margolin and co-workers[2] found that simple unsaturated aliphatic carbinols possessed a high degree of activity, satisfactory duration of action, and low toxicity. Methyl parafynol (Dormison) was considered one of the most promising of these unsaturated carbinols. Chemically it is 3-methyl-pentyne-ol-3 and its structural formula is:



This compound is of considerable pharmacologic interest because the fate of the ethinyl group in body metabolism remains unknown. Inactivation of the drug depends upon destruction of this group.[3]

3-methyl-pentyne-ol-3 has a high selectivity of action. It is not analgesic. It is not anesthetic when administered intravenously in sublethal amounts. It does not appear to be antispasmodic. In contrast to the barbiturates and other hypnotics, even in large doses it does not depress respiration. Caffeine given parenterally causes rapid recovery from the deep hypnotic state caused by the drug and no undesirable after-effects have been observed in animals given overdoses of the drug. 3-methyl-pentyne-ol-3 was tested for chronic toxicity in rats and dogs with daily doses of 200 to 300 mg. per kilogram of body weight (approximately 70 times the recommended human dose). The amount of sugar in the blood, hemoglobin, the number of erythrocytes and leukocytes, and the leukocyte differential remained normal. Dogs had normal renal function when tested for phenolsulfonphthalein excretion.

Dormison is rapidly inactivated in the body. The content of the drug in the blood decreases rapidly although only small amounts are excreted in the urine. The drug is most rapidly inactivated by hepatic and renal tissue. Evanescence of the activity is associated with enzymatic modification of the ethinyl group.[2]

In a clinical study of 134 patients,[2] 3-methyl-pentyne-ol-3 was found to be an effective hypnotic without toxic effects, and free from undesirable side actions. The effective oral dose is 200 to 300 mg. No residual effect was reported on awakening. Some patients, given the drug for over six months, had no untoward symptoms. Before and after the drug was given, studies to determine the cell content of the blood and the amounts of urea nitrogen, creatinine, total serum protein, albumin, globulin, phosphorus, alkaline phosphatase, and cholesterol (free and combined) were carried out. The icteric index was observed and van den Bergh, thymol turbidity or cephalin flocculation tests were done. The urine also was examined before and after medication. No changes attributable to the drug were observed.

The following case appears to be the first reported of toxic reaction to Dormison.

CASE REPORT

The patient, a Caucasian woman 43 years of age, had redness and blistering of the skin, with a severe burning sensation, and pain in the joints. The condition had existed for three days.

On December 13, 1951, the patient, having read about Dormison in a popular magazine, obtained several capsules of it and that night took two of them for sleep. The next day mild transient itching and red spots on the skin developed. Again she took two capsules that night. The itching and redness were more severe the following day; but still she did not associate the condition with the drug, and at bedtime, because the itching and discomfort were intense,

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